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| 13. SUPPLEMENTARY NOTES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                  |                         |                            |                                                          |                                           |
| 14. ABSTRACT<br>A randomized, double-blinded, placebo-controlled clinical trial was conducted to evaluate the effectiveness of propranolol, topiramate, and amitriptyline as treatments for chronic post-traumatic headaches secondary to combat-related mild head injury. Over a 3-year period 305 soldiers with chronic PTH were screened and 64 were enrolled, falling short of the enrollment target of 240 subjects. 39 (61%) had evaluable data after drug titration and 34 (53%) completed the 3-month treatment period. Discontinuation rates ranged from 39% for topiramate to 53% for amitriptyline but were not significantly different between treatment arms. Monthly headache days decreased from 12.2 at baseline to 7.9 during the final month in all subjects (-36%, p=0.0001), 16.7 to 8.7 in the placebo arm (-48%, p=0.012), 11.7 to 6.1 in the amitriptyline arm (-41%, p=0.0005), 14.0 to 8.3 in the propranolol arm (-41%, p=0.10), and 9.3 to 8.8 in the topiramate arm (-5%, p=0.80). Mean MIDAS scores decreased from 71 at baseline to 31 at the final visit among all subjects (p=0.0001) and significantly declined in the placebo, topiramate, and propranolol arms. There were no significant differences between placebo and any treatment. PTSD symptom checklist scores significantly declined in the topiramate arm. This study is limited by the small number of subjects, high response rate in the placebo arm, and relatively low subject completion rate. The study is closed. |                  |                         |                            |                                                          |                                           |
| 15. SUBJECT TERMS<br>Headache, mild head trauma, concussion, treatment, clinical trial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                  |                         |                            |                                                          |                                           |
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## **Introduction**

Headaches are the most common symptom after mild traumatic brain injury (1-4). Chronic post-traumatic headaches (PTHAs) develop in 20% of TBI victims, contributing to disability, healthcare utilization, and poor quality of life (5-6). There are no prospective, controlled clinical trials evaluating medical treatments for chronic post-traumatic headaches (7).

The purpose of this study was to determine the effectiveness of propranolol, amitriptyline, and topiramate as treatments for chronic PTHAs. We conducted a single-center, prospective, randomized, double-blind, placebo-controlled, multi-arm trial to evaluate propranolol, amitriptyline, and topiramate for treatment of chronic PTHAs. The enrollment target was 240 patients meeting International Classification of Headache Disorders (ICHD) diagnostic criteria for chronic post-traumatic headaches. Subjects were recruited from the Traumatic Brain Injury Program and the Neurology Clinic at Madigan Army Medical Center, Ft. Lewis, WA. Study participants were U.S. Army soldiers with chronic post-traumatic headaches attributable to mild traumatic head injury sustained while deployed to a combat theater. Participants were randomized to receive placebo, propranolol 80 mg daily dose, amitriptyline 50 mg daily dose, or topiramate 100 mg daily dose for 3 months. The primary outcome measure was the number of moderate-severe headache days during the third month of treatment. Secondary outcome measures included the proportion of subjects with at least a 50% reduction in headache frequency, headache-related disability as measured by the Headache Impact Test (HIT-6) and Migraine Disability Assessment Scale (MIDAS), PTSD symptom checklist score, and medication tolerability. The findings of this study will improve the care of patients with chronic headaches after traumatic brain injury.

## **Body:**

Over the 3.5-year study period, 305 soldiers were screened for study enrollment and 64 were enrolled. Of these, 39 (61%) had evaluable data after drug titration and 34 (53%) completed the 3-month treatment period. Discontinuation rates ranged from 39% for topiramate to 53% for amitriptyline but were not significantly different between treatment arms. The most commonly identified reason for a subject discontinuing the study was that he moved away from the geographic region. No serious adverse events occurred.

Monthly headache days decreased from 12.2 at baseline to 7.9 during the final month in all subjects (-36%,  $p=0.0001$ ), 16.7 to 8.7 in the placebo arm (-48%,  $p=0.012$ ), 11.7 to 6.1 in the amitriptyline arm (-41%,  $p=0.0005$ ), 14.0 to 8.3 in the propranolol arm (-41%,  $p=0.10$ ), and 9.3 to 8.8 in the topiramate arm

(-5%,  $p=0.80$ ).  $\geq 50\%$  responder rates were 49% (19/39) for all subjects, 50% (3/6) for placebo, 67% (8/12) for amitriptyline, 44% (4/9) for propranolol, and 33% (4/12) for topiramate. Responder rates were 49% (19/39) for all subjects, 50% (3/6) for placebo, 67% (8/12) for amitriptyline, 44% (4/9) for propranolol, and 33% (4/12) for topiramate. Mean MIDAS scores decreased from 71 at baseline to 31 at the final visit among all subjects ( $p=0.0001$ ) and significantly declined in the placebo, topiramate, and propranolol arms. HIT-6 scores and PTSD symptom checklist scores significantly declined in the topiramate arm only.

### **Key Research Accomplishments:**

1. 64 subjects were enrolled, randomized, started on one of the study medications, and monitored for follow-up outcomes.
2. Follow-up of all enrolled study subjects was completed. The study is closed.
3. A study database was generated and analyzed.
4. An abstract reporting the study findings was accepted for presentation at the 2012 American Academy of Neurology meeting in April, 2012.

### **Reportable Outcomes:**

1. An abstract of the study findings has been accepted for presentation at the 2012 American Academy of Neurology meeting in April, 2012.
2. Erickson JC, Neely E, Theeler BJ. Post-traumatic Headache. *Continuum: Lifelong Learning in Neurology*. December, 2010; Vol 16(6):55-78. (8)

### **Conclusion:**

This study is limited by the small sample size and unexpectedly high response rate in the placebo arm. Amitriptyline, propranolol, and topiramate were similarly tolerated and were associated with significant improvements in headache frequency and/or headache-related disability but no treatment was superior to placebo. Topiramate was also associated with a significant improvement in PTSD symptoms. The slow enrollment rate of subjects and the high discontinuation rate (47%) reveal significant challenges in conducting a 4-month study in military service members. The findings will be useful for designing large, multi-center clinical trials to conclusively evaluate the efficacy of headache prophylactic therapies for chronic PTH in military personnel.

## References:

1. Packard RC. Epidemiology and pathogenesis of posttraumatic headaches. *J Head Trauam Rehabil* 1999;14: 9-21.
2. Uomoto JM, Esselman PC. Traumatic brain injury and chronic pain: differential types and rates by head injury severity. *Arch Phys Med Rehabil* 1993;74: 61-64.
3. Lahz S, Bryant RA. Incidence of chronic pain following traumatic brain injury. *Arch Phys Med Rehabil* 1996;77: 889-891.
4. Walker WC, Seel RT, Curtiss G, Warden DL. Headache after moderate and severe traumatic brain injury: a longitudinal analysis. *Arch Phys Med Rehabil* 2005;86:1793-1800.
5. Packard RC, Ham LP. Posttraumatic headache: determining chronicity. *Headache* 1993;33: 133-4.
6. Baandrup L, Jensen R. Chronic post-traumatic headache- a clinical analysis in relation to the International Headache Classification 2<sup>nd</sup> edition. *Cephalalgia* 2005;25: 132-138.
7. Lew HL, Lin PH, Fuh JL, Wang SJ, Clark DJ, Walker WC. Characteristics and treatment of headache after traumatic brain injury: A focused review. *Am J Phys Med Rehabil* 2006;85:619-627.
8. Erickson JC, Neely E, Theeler BJ. Post-traumatic Headache. *Continuum: Lifelong Learning in Neurology*. December, 2010; Vol 16(6):55-78.

## Supporting Data:

**Table 1. Number of subjects in each treatment arm.**

| Treatment     | #Randomized | # completing drug titration | #Completing study |
|---------------|-------------|-----------------------------|-------------------|
| Placebo       | 12          | 6 (50%)                     | 6 (50%)           |
| Topiramate    | 18          | 12 (67%)                    | 11 (61%)          |
| Propranolol   | 17          | 9 (53%)                     | 9 (53%)           |
| Amitriptyline | 17          | 12 (71%)                    | 8 (47%)           |
| All           | 64          | 39 (61%)                    | 34 (53%)          |

**Table 2. Responder rates in each treatment arm.**

| Treatment     | Responders ( $\geq 50\%$ decrease) |
|---------------|------------------------------------|
| Placebo       | 3/6 (50%)                          |
| Topiramate    | 4/12 (33%)                         |
| Propranolol   | 4/9 (44%)                          |
| Amitriptyline | 8/12 (67%)                         |
| All           | 19/39 (49%)                        |

**Table 3. Change in monthly headache days.**

| Treatment     | n  | Mean Monthly HA days/month (SD) |             |        | % Change | Paired t-test |
|---------------|----|---------------------------------|-------------|--------|----------|---------------|
|               |    | Baseline                        | Final       | Change |          |               |
| Placebo       | 6  | 16.67                           | 8.67        | -8.0   | -48%     | 0.0121        |
| Topiramate    | 12 | 9.25*                           | 8.83        | -0.42* | -5%      | 0.80          |
| Propranolol   | 9  | 14.0                            | 8.33        | -5.67  | -41%     | 0.10          |
| Amitriptyline | 12 | 11.67                           | 6.08        | -5.58  | -41%     | 0.0005        |
| All           | 39 | 12.23 (6.39)                    | 7.85 (6.21) | -4.38  | -36%     | 0.0001        |

p=0.01 compared to placebo

**Table 4. Headache-related disability as measured by the MIDAS and HIT-6.**

| Treatment     | MIDAS       |              |          | HIT-6       |              |          |
|---------------|-------------|--------------|----------|-------------|--------------|----------|
|               | Baseline    | Final        | paired t | Baseline    | Final        | paired t |
| Placebo       | 83.17       | 27.83        | 0.008    | 63.17       | 51.33        | 0.122    |
| Topiramate    | 62.27       | 25.00        | 0.019    | 61.6        | 56.5         | 0.046    |
| Propranolol   | 68.5        | 29.13        | 0.046    | 64.38       | 53.5         | 0.167    |
| Amitriptyline | 75.0        | 45.86        | 0.21     | 55.7        | 52.0         | 0.32     |
| All (n=32)    | 70.53(47.8) | 31.13(38.28) | 0.0001   | 61.29(5.92) | 53.71(13.62) | 0.0034   |

**Table 5. Depression symptoms (PHQ-9) and PTSD symptoms (PCL).**

| Treatment     | PHQ-9       |            |          | PCL          |              |          |
|---------------|-------------|------------|----------|--------------|--------------|----------|
|               | Baseline    | Final      | paired t | Baseline     | Final        | paired t |
| Placebo       | 13.17       | 10.5       | 0.39     | 49.0         | 45.8         | 0.63     |
| Topiramate    | 11.45       | 9.82       | 0.55     | 48.1         | 38.3         | 0.0495   |
| Propranolol   | 10.0        | 8.75       | 0.32     | 42.3         | 37.1         | 0.40     |
| Amitriptyline | 8.29        | 8.00       | 0.87     | 37.7         | 36.1         | 0.66     |
| All (n=32)    | 10.72(4.84) | 9.28(7.06) | 0.21     | 44.2 (16.21) | 38.9 (17.75) | 0.047    |

**Appendices: none**